Exploring the relationships of gamma-hydroxybutyrate and sleep on metabolism, physiology, and behavior in humans

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CHAPTER 3

Sodium Oxybate for Excessive Daytime Sleepiness in Parkinson Disease - An Open-Label Polysomnographic Study

Archives of Neurology (2008) 65(10): 1337-1340

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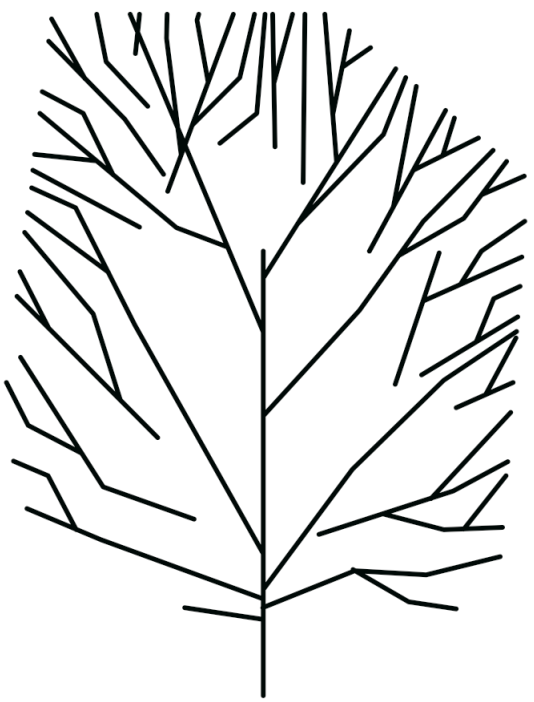

Abstract

Background	Many patients with Parkinson disease (PD) have excessive daytime sleepiness and numerous nocturnal sleep abnormalities.
Objective	To determine the safety and efficacy of the controlled drug sodium oxybate in a multicenter, open-label, polysomnographic study in subjects with PD and sleep disorders.
Design, Setting, and Patients	Inclusion required an Epworth Sleepiness Scale (ESS) score greater than 10 and any subjective nocturnal sleep concern, usually insomnia. An acclimation and screening polysomnogram was performed to exclude subjects with sleep-disordered breathing. The following evening, subjects underwent another polysomnogram, followed by an evaluation with the Unified Parkinson Disease Rating Scale (UPDRS) while practically defined off ("off") PD medications, ESS (primary efficacy point), Pittsburgh Sleep Quality Inventory, and Fatigue Severity Scale. Subjects then started sodium oxybate therapy, which was titrated from 3 to 9 g per night in split doses (at bedtime and 4 hours later) across 6 weeks and returned for subjective sleep assessments. They then returned at 12 weeks after initiating therapy for a third polysomnogram, an off-medication UPDRS evaluation, and subjective sleep assessments. Data are expressed as mean (SD).
Results	We enrolled 38 subjects. At screening, 8 had sleep apnea (n=7) or depression (n= 1). Twenty-seven of 30 subjects completed the study. Three dropped out owing to dizziness (n=3) and concurrent depression (n = 1). The mean dose of sodium oxybate was 7.8 (1.7) g per night. The ESS score improved from 15.6 (4.2) to 9.0 (5.0) (P<.001); the Pittsburgh Sleep Quality Inventory score, from 10.9 (4.0) to 6.6 (3.9) (P<.001); and the Fatigue Severity Scale score, from 42.9 (13.2) to 36.3 (14.3) (P<.001). Mean slow-wave sleep time increased from 41.3 (33.2) to 78.0 (61.2) minutes (P = .005). Changes in off-medication UPDRS scores were not significant, from 28.3 (10.3) to 26.2 (9.6).
Conclusion	Nocturnally administered sodium oxybate improved excessive daytime sleepiness and fatigue in PD.
Trial Registration:	clinicaltrials.gov Identifier: NCT00641186

Introduction

Parkinson's Disease (PD) is strongly associated with the following 2 broad categories of sleep abnormalities: excessive daytime sleepiness (EDS) and nocturnal sleep dysfunction. Excessive daytime sleepiness has been well demonstrated using the subjective Epworth Sleepiness Scale (ESS) and objective polysomnography (PSG), including multiple sleep latency testing. The consequences of EDS, however, are sometimes difficult to segregate clearly from fatigue, lethargy, and depression, all of which are also common in PD.

Excessive daytime sleepiness in PD has generally been associated with greater age, more advanced disease, and dopaminergic drug use.[1-5] Therefore, both PD and its treatment can cause EDS. Nocturnal sleep in PD is also markedly abnormal. Documented problems include fragmented sleep with multiple arousals and/or full awakenings associated with rigidity, dystonia, tremor, pain, sialorrhea, and nocturia[6-8]; rapid eye movement sleep behavior disorder[9-11]; periodic limb movements[12,13]; restless legs syndrome[14]; and sleep apnea.[15] Some of these may precede the motor symptoms of PD by many years. Intrinsic changes in sleep architecture are less marked but include reduced slow-wave sleep (SWS) and reduced sleep spindles.[16,17] Although it seems intuitive, studies have not confirmed a correlation between nocturnal sleep dysfunction and EDS in PD.[16,18] Relatively little therapeutic research has addressed these problems. Modafinil[19-21] has been demonstrated to have some benefit for EDS in patients with PD, although the improvement was modest. To our knowledge, no reported therapeutic studies have carefully evaluated a specific treatment for nocturnal sleep problems in the PD population.

Sodium oxybate (Xyrem; Jazz Pharmaceuticals, Inc.) is a unique compound approved by the US Food and Drug Administration for the treatment of cataplexy and EDS in patients with narcolepsy.[22,23] Owing to the potential for abuse, especially when mixed with alcohol (this is a salt of gamma-hydroxybutyrate, the "date rape drug"), use of sodium oxybate is restricted through a central pharmacy registry. Sodium oxybate is a metabolite of 7-aminobutyric acid, although it may be an independent endogenous neurotransmitter, with a very short half-life and short clinical effect, usually 2.5 to 4.0 hours. Therefore, 2 doses are used to achieve a typical full night of sleep, one at initiation of sleep and the other 4 hours later. Polysomnographic studies show a consistent increase in SWS in subjects with normal sleep24 and in those with sleep abnormalities.[25] We evaluated the use of sodium oxybate for EDS in subjects with PD in a multicenter, open-label, PSG study.

Methods

Subjects were recruited from the Baylor College of Medicine Parkinson Disease Center and Movement Disorder Clinic and Raleigh Neurology Associates. The protocol was approved by the Baylor College of Medicine Institutional Review Board and the Western Institutional Review Board. All subjects signed informed consent.

We enrolled subjects with PD, aged 30 to 75 years, with Hoehn and Yahr stages 1.5 to 4.0 during periods while practically defined off ("off") medication, Mini-Mental State Examination scores of greater than 24, ESS scores of greater than 10, and a patient report of unsatisfactory sleep. This could include any sleep concern, but always resulted in some insomnia. The subjects could not be taking medications with known central nervous system-depressant properties and had been receiving stable PD medications for at least 30 days before and throughout the study. We excluded subjects with serious medical conditions, including renal insufficiency or congestive heart failure, depression (Beck Depression Inventory score, > 16), or known sleep apnea or narcolepsy.

The subjects underwent a screening/acclimation PSG. They were subsequently excluded if they had more than mild sleep apnea (apnea/hypopnea index >15) and oxygen desaturation levels consistently below 90%. Obstructive apneas were scored as 10 seconds of more than 90% airflow reduction with continued respiratory effort. Obstructive hypopneas were scored as 10-second epochs of more than 30% airflow reduction associated with either a 3% oxygen desaturation or an electro-encephalographic arousal.

Within 7 days, the subjects underwent the entry PSG. They returned to the clinic the following morning without taking their usual PD medications (off-medication state) and underwent assessment with the Unified Parkinson Disease Rating Scale (UPDRS). After taking their PD medications, they completed the Fatigue Severity Scale (FSS), Pittsburgh Sleep Quality Inventory (PSQI), the 36-Item Short Form Health Survey quality-of-life assessment, and the ESS (primary efficacy point). The subjects then started sodium oxybate therapy, 4.5 g per night, to be taken in 2 equally divided doses: 2.25 g (4.5 mL) at bedtime, and 2.25 g (4.5 mL) 2.5 to 4.0 hours later. They woke naturally or set an alarm for their second dose. A follow-up telephone call 1 week later reviewed medication adherence and any possible adverse effects. The subjects were examined after 2 weeks of therapy with reevaluations of the ESS score, vital signs, and adverse events. The dose was increased to 6 g per night, to be taken in 2 equally divided doses. After another follow-up telephone call and according to the clinical judgment of site investigators, the dose was increased weekly by 1.5-g increments to a maximum nightly dose of 9.0 g. In the event that adverse effects developed with the higher doses, the dose could be reduced to a tolerated level for the remainder of the trial. The final clinic visit (study day 56) included a final PSG, followed by an off-medication UPDRS evaluation, then a repeated battery of tests after PD medication therapy was restored. The subjects returned all unused drug.

The primary efficacy point was change in the ESS score (daytime sleepiness). Other measures of daytime symptoms (the ESS score) and nocturnal symptoms (the polysomnogram and PSQI) were secondary measures. Statistics included descriptive calculations and paired, 2-tailed t tests. Significance was set at $P < .05$. Study design, data management, database design, statistical analysis, and manuscript drafting were all performed by the primary investigator (W.G.O.), who maintains ownership of the data. The primary investigator received an

Investigational New Drug exemption from the US Food and Drug Administration for the study. Unless otherwise specified, data are expressed as mean (SD).

Results

Thirty-eight subjects with PD were enrolled to achieve 30 successful screenings. We excluded 8 subjects at screening secondary to sleep apnea criteria (n = 7) and depression (n= 1). Three subjects dropped out after randomization for dizziness (n = 3) and concurrent depression (n= 1); two of these dropped out before any follow-up data were collected and were therefore excluded from the efficacy analysis. The 6-week subjective sleep data in the third subject were included as the last observation carried forward.

The mean age of the 30 subjects (of whom 24 were men) was 61.5 (8.7) years, and the duration of PD was 8.6 (5.5) years (range, 1-25 years). The Hoehn and Yahr stages were 2.0 (n = 14), 2.5 (n=11), and 3.0 (n = 5). Twenty-seven subjects were white, 2 were Hispanic, and 1 was Asian. The mean entry Mini-Mental State Examination score was 29.1 (1.3) (range, 25-30). All subjects were treated with a dopamine agonist without levodopa (n = 8), levodopa without a dopamine agonist (n = 3), or levodopa and a dopamine agonist (n = 19). Six of the subjects taking levodopa and a dopamine agonist also took a monoamine oxidase type B inhibitor; 10 subjects took a catechol-O-methyl-transferase inhibitor; and 11 subjects took amantadine hydrochloride.

The mean final dose of sodium oxybate was 7.8 (1.7) g per night. The final nightly doses were 3.0 g (n = 2),4.5 g (n=1), 6.0 g (n = 6), 7.5 g (n = 4), and 9.0 g (n=17).

The ESS, PSQI, and FSS scores improved significantly. Changes in the 36-Item Short Form Health Survey score were not significant (**Table 1**).

Slow-wave sleep time increased in 27 subjects, (P= .005) (**Table 2**), whereas rapid eye movement sleep time was modestly reduced. Total apneas mildly increased, but the mean and maximum oxygen desaturation values did not change. No other PSG features changed significantly. Increased SWS time (in minutes) did not correlate with reduced ESS scores (r=0.10; P=.09).

Mean off-medication morning UPDRS motor scores were stable in 27 subjects, changing from 28.4 (10.3) to 26.2 (9.6) (NS). No subject subjectively reported that there was any meaningful change in his or her motor symptoms.

Adverse events probably or definitely related to the drug included dizziness (n=3), nocturia/enuresis (n=3), nausea (n=1), daytime sleepiness (n=1), reduced alertness (n=1), and rebound morning tremor (n=1). One subject reported increased morning tremor. Additional adverse events that were considered not related to the study drug included constipation (n=1), 1 delusions (n =1),1 and, in a single subject, bradycardia, anxiety, depression, and edema. Twenty-two of 30 subjects (73%) reported no adverse events.

At the study's conclusion, 18 of 27 subjects (67%) completed application forms for the central distribution pharmacy to continue sodium oxybate therapy.

TABLE 1. Sleep and Fatigue Results[a]

	Mean (SD) Score		
Instrument	**Before Sodium Oxybate Therapy**	**After Sodium Oxybate Therapy**	**P Value**
ESS	15.6 (4.2)	9.0 (5.0)	<.001
PSQI	10.9 (4.0)	6.6 (3.9)	<.001
FSS	42.9 (13.2)	36.3 (14.3)	<.001
SF-36	95.7 (7.1)	92.3 (5.1)	.71

Abbreviations: ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; PSQI, Pittsburgh Sleep Quality Inventory; SF-36, 36-Item Short Form Health Survey. [a]Findings are reported for 28 subjects.

TABLE 2. PSG Results in 27 Subjects with Parkinson Disease

	Mean (SD) Findings		P Value
	Before Sodium Oxybate Therapy	**After Sodium Oxybate Therapy**	
Total sleep time, min	363 (65)	353 (74)	.11
Stage 1, min	40 (45)	34 (44)	.23
Stage 2, min	215 (88)	197 (78)	.27
Stages 3-4, min	41 (33)	78 (61)	.005
REM sleep, min	57 (39)	37 (24)	.002
Sleep efficiency, %	75 (14)	74 (15)	.29
Total No. of PLMs	14 (14)	22 (30)	.13
Total apnea /hypoapnea index[a]	7 (6)	13 (12)	.004
Mean oxygen saturation level, %	93.9 (2.5)	94.1 (2.3)	.68
Minimum oxygen saturation level, %	88.3 (3.5)	87.0 (3.6)	.44
No. of awakenings	57 (42)	59 (77)	.69

Abbreviations: PLMs, periodic limb movements; PSG, polysomnography; REM, rapid eye movement. [a]Calculation of the index is explained in the "Methods" section.

Comment

Overall, nocturnally administered sodium oxybate was well tolerated, increased SWS, and improved subjective nighttime and daytime sleep problems and daytime fatigue in subjects with PD. Improvements in ESS were similar to or better than those found when the drug is used as therapy for narcolepsy.[22,23] The PD motor features were unchanged.

The mechanism by which sodium oxybate improves EDS is not known. It is known to increase SWS;[26] however, our study did not show a significant correlation between improved SWS and ESS scores. The SWS change in our study compared only two nights and is variable. In addition, our study was not powered in any way to specifically address this question, so we cannot entirely exclude the possibility of SWS variations. Sodium oxybate has also been postulated to improve EDS by decreasing sleep fragmentation in narcolepsy trials[25]; however, we found improved EDS without reduced awakenings in this PD study. Furthermore, deep brain stimulation of the subthalamic nucleus improves sleep fragmentation associated with nocturnal motor abnormalities in subjects with PD but has not improved EDS in a small number of studied subjects.[27]

As an alternative explanation, nocturnal sodium oxybate use may result in the rebound vigilant state observed during the day after nighttime administration. The short half-life of sodium oxybate allows for complete washout by the morning, when increased release of stored dopamine and norepinephrine may occur and contribute to the observed enhanced wakefulness.[28,29] Dopamine release is actually inhibited while the drug is active, which may account for the nonsignificant increase in periodic limb movements.[30] We did not believe that the slight increase in apnea was clinically meaningful, but this needs to be monitored. There was no evidence of abuse.

This study has all of the shortcomings of any open-label trial. We intentionally designed broad inclusion criteria and did not exclude subjects with restless legs syndrome or rapid eye movement sleep behavior disorder, neither of which appears to affect EDS in PD.[14] Given the robust efficacy and good tolerability of the study drug and the lack of effective treatment for EDS in patients with PD, we believe that controlled trials using objective measures of daytime sleepiness are justified.

Author Contributions

Study concept and design: Ondo. Acquisition of data: Ondo, Perkins, Swick, Hull, Jimenez, Garris, and Pardi. Analysis and interpretation of data: Ondo. Drafting of the manuscript: Ondo. Critical revision of the manuscript for important intellectual content: Ondo, Perkins, Swick, Hull, Jimenez, Garris, and Pardi. Statistical analysis: Ondo. Administrative, technical, and material support: Ondo, Perkins, Swick, Hull, Jimenez, Garris, and Pardi. Obtained funding: Ondo. Study supervision: Ondo.

Financial Disclosure

Dr. Ondo has received research grant support from Jazz Pharmaceuticals, Inc; is a member of the speaker's bureau for Allergan, Boehringer Ingelheim, GlaxoSmithKline, TEVA, UCB Pharma, and Valeant; and has received research funding from Allergan, Boehringer Ingelheim, Forest, Schwartz Pharmaceuticals, and Valeant. Dr. Perkins is a member of the speaker's bureau for Boehringer Ingelheim, Cephalon, GlaxoSmithKline, and Jazz Pharmaceuticals, Inc; and has received research support and has served on the professional advisory board for Jazz Pharmaceuticals, Inc. Dr. Swick is a member of the speaker's bureau for Boehringer Ingelheim, Cephalon, GlaxoSmithKline, Jazz Pharmaceuticals, Inc, Sanofi-Aventis, Sepracor, and Takeda Pharmaceuticals; has received research support from Cephalon, GlaxoSmithKline, Jazz Pharmaceuticals, Inc, Merck, Pfizer, Sanofi-Aventis, Somazon, and Takeda; and has served on the professional advisory board for Jazz Pharmaceuticals, Inc. Mr. Pardi is an employee of Jazz Pharmaceuticals, Inc, and provided assistance in the analysis of the data and the review of the manuscript. Funding/Support: This study was supported by an unrestricted research grant and supply of the study drug from Jazz Pharmaceuticals, Inc.

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